



Innovation

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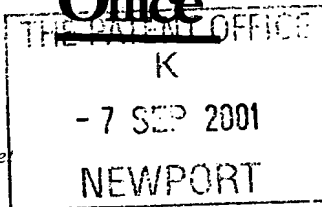
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# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference	PHAZ / P24850GB		
2. Patent number (The)	0121611.8	7 SEP 2001	07SEP01 E658186-1 002846 P01/7700 0.00-0121611.8
3. Full name, address and postcode of the or of each applicant (underline all surnames)	<b>Pharmacore AB</b> c/o Projipharma AB Lagerlöfsgatan 8, 1 tr. SE-112 60 Stockholm Sweden <i>c/o A-H Science Invest AB  PO Box 3096  SE-400 10 GÖTEBORG  SWEDEN</i>		
Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its incorporation	Sweden	815 1158 001	22/10/01
4. Title of the invention	PHARMACEUTICALLY-USEFUL COMPOUNDS		
5. Name of your agent (if you have one)	<b>ERIC POTTER CLARKSON</b> <b>PARK VIEW HOUSE</b> <b>58 THE ROPEWALK</b> <b>NOTTINGHAM</b> <b>NG1 5DD</b>		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)			
Patents ADP number (if you know it)	1305010		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:	YES		
a) any applicant named in part 3 is not an inventor; or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d))			

# Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 39 ✓

Claims(s) 10 ✓

Abstract 1 ✓

Drawing(s) 0

10. If you are also filing in any of the following, state how many against each item.

Priority Documents 0

Translations of priority documents 0

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*) NO

Request for preliminary examination and search (*Patents Form 9/77*) NO

Request for substantive examination (*Patents Form 10/77*) NO

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

ERIC POTTER CLARKSON

Date

6 September 2001

12. Name and daytime telephone number of person to contact in the United Kingdom

0115 9552211

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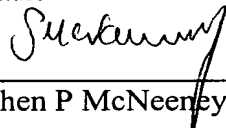
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**Statement of inventorship and of  
right to grant of a patent**

PATENT OFFICE

21 NOV 2001  
NEWPORT

1.	Your reference	PHAZ/P24850GB
2.	Patent application number (if you know it)	0121611.8
3.	Full name of the or of each applicant	Pharmacore AB
4.	Title of the invention	Pharmaceutically-Useful Compounds
5.	State how the applicant(s) derived the right from the inventor(s) to be granted a patent	By virtue of assignment
6.	How many, if any, additional Patents Forms 7/77 are attached to this form (see note (c))	None
7.	I/We believe that the person(s) named over the page (and on any extra copies of this form) is/are the inventor(s) of the invention which the above patent application relates to.	
	Signature	Date
		20 November 2001
8.	Name and daytime telephone number of person to contact in the United Kingdom	Stephen P McNeeney – (0115) 9552211

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Enter the full name, address and postcodes of the inventors in the boxes and underline the surnames

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Patents ADP number (if you know it):

08273205001

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Patents ADP number (if you know it):

08272213001

**Reminder**

**Have you signed the form?**

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## PHARMACEUTICALLY-USEFUL COMPOUNDS

### Field of the Invention

5 This invention relates to novel pharmaceutically-useful compounds, in particular compounds that are angiotensin II (AngII) agonists, more particularly agonists of the AngII type 2 receptor (hereinafter the AT2 receptor), and especially agonists that bind selectively to that receptor. The invention further relates to the use of such compounds as medicaments, to  
10 pharmaceutical compositions containing them, and to synthetic routes to their production.

### Background and Prior Art

15 The endogenous hormone AngII is a linear octapeptide (Asp<sup>1</sup>-Arg<sup>2</sup>-Val<sup>3</sup>-Tyr<sup>4</sup>-Ile<sup>5</sup>-His<sup>6</sup>-Pro<sup>7</sup>-Phe<sup>8</sup>), and is the active component of the renin-angiotensin system (RAS). It is produced by the sequential processing of the pro-hormone angiotensinogen by renin and angiotensin converting enzyme (ACE).

20

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure, body fluid and electrolyte homeostasis. Ang II exerts these physiological actions in many organs including the kidneys, the adrenal glands, the heart, blood vessels, the brain, the gastrointestinal tract  
25 and the reproductive organs (de Gasparo *et al*, *Pharmacol. Rev.* (2000) **52**, 415-472).

Two main classes of AngII receptors have been identified, and designated as the type 1 receptor (hereinafter the AT1 receptor) and the AT2 receptor.

30 The AT1 receptor is expressed in most organs, and is believed to be

responsible for the majority of the biological effects of AngII. The AT2 receptor is more prevalent than the AT1 receptor in fetal tissues, the adult ovaries, the adrenal medulla and the pancreas. An equal distribution is reported in the brain and uterus (Ardaillou, *J. Am. Soc. Nephrol.*, **10**, S30-39 (1999)).

Several studies in adult individuals appear to demonstrate that, in the modulation of the response following AngII stimulation, activation of the AT2 receptor has opposing effects to those mediated by the AT1 receptor.

The AT2 receptor has also been shown to be involved in apoptosis and inhibition of cell proliferation (see de Gasparo *et al, supra*). Further, it seems to play a role in blood pressure control. For example, it has been shown in transgenic mice lacking AT2 receptors that their blood pressure was elevated. Furthermore, it has been concluded that the AT2 receptor is involved in exploratory behaviour, pain sensitivity and thermoregulation.

The expression of AT2 receptors has also been shown to increase during pathological circumstances, such as vascular injury, wound healing and heart failure (see de Gasparo *et al, supra*).

The expected pharmacological effects of agonism of the AT2 receptor are described generally in de Gasparo *et al, supra*.

More recently, AT2 receptor agonists have been shown to be of potential utility in the treatment and/or prophylaxis of disorders of the alimentary tract, such as dyspepsia and irritable bowel syndrome, as well as multiple organ failure (see international patent application WO 99/43339).



AngII antagonists (which bind to the AT1 and/or AT2 receptors) have been disclosed in *inter alia* European patent application EP 512 675; international patent applications WO 94/27597, WO 94/02142, WO 95/23792 and WO 94/03435; and US patent numbers 5,091,390, 5,177,074,  
5 5,412,097, 5,444,067, 5,520,521, 5,260,285, 5,376,666, 5,252,574, 5,312,820, 5,330,987, 5,166,206, 5,932,575 and 5,240,928. AngII agonists, and particularly AT2 receptor agonists, are not contemplated in any of these documents.

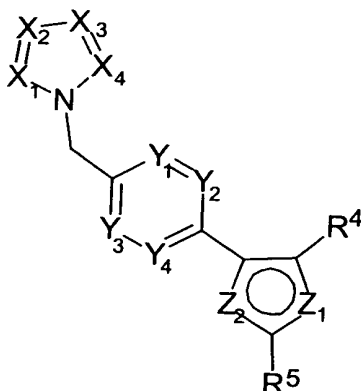
10 International patent application WO 00/68226 and US patent number 6,235,766 disclose compounds comprising substituted imidazolyl groups, which groups are attached, *via* a methylene bridge, to a phenylthiophene moiety, as agonists of angiotensin-(1-7) receptors. The use of the compounds as Ang II receptor agonists is neither mentioned nor suggested.

15 Peptide and non-peptide AT2 receptor agonists, unrelated structurally to those described herein, and potential uses thereof, have been disclosed in, for example, international patent applications WO 00/38676, WO 00/56345, WO 00/09144, WO 99/58140, WO 99/52540, WO 99/46285, WO  
20 99/45945, WO 99/42122, WO 99/40107, WO 99/40106, WO 99/39743, WO 99/26644, WO 98/33813, WO 00/02905 and WO 99/46285; US patent number 5,834,432; and Japanese patent application JP 143695.

However, there remains a need for effective and/or selective AT2 receptor  
25 agonists, which are expected to find utility in *inter alia* the above-mentioned conditions.

### Disclosure of the Invention

30 According to the invention there is provided a compound of formula I,



wherein

- 5 one of  $X_1$  and  $X_2$  represents  $-N-$  and the other represents  $-C(R^1)-$ ;  
 $X_3$  represents  $-N-$  or  $-C(R^2)-$ ;  
 $X_4$  represents  $-N-$  or  $-C(R^3)-$ ;  
 $R^1, R^2$  and  $R^3$  independently represent H,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  
 $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl or halo;
- 10 provided that, when  $X_1$  represents  $-C(R^1)-$ ,  $X_3$  represents  $-C(R^2)-$  and  $X_4$   
represents  $-C(R^3)-$ , then  $R^1$  represents H;  
 $Y_1, Y_2, Y_3$  and  $Y_4$  represent  $-CH-$ ,  $-CF-$  or  $-N$ , provided that, at any one  
time, no more than two of  $Y_1, Y_2, Y_3$  and  $Y_4$  may represent  $-N-$ ;
- 15  $Z_1$  represents  $-CH-$ ,  $-O-$ ,  $-S-$ ,  $-N-$  or  $-CH=CH-$ ;  
 $Z_2$  represents  $-CH-$ ,  $-O-$ ,  $-S-$  or  $-N-$ ;  
provided that:
  - (a)  $Z_1$  and  $Z_2$  are not the same;
  - (b) when  $Z_1$  represents  $-CH=CH-$ , then  $Z_2$  may only represent  $-CH-$  or  
 $-N-$ ; and
  - 20 (c) when one  $Z_1$  and  $Z_2$  represents  $-CH-$ , then the other represents  $-O-$   
or  $-S-$ ;

$R^4$  represents  $-S(O)_2N(H)C(O)R^6$ ,  $-C(O)N(H)S(O)_2R^6$ , or, when  $Z_1$  represents  $-CH=CH-$ ,  $R^4$  may represent  $-N(H)S(O)_2N(H)C(O)R^7$  or  $-N(H)C(O)N(H)S(O)_2R^7$ ; and

$R^5$  represents  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy or  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl;

5  $R^6$  represents  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl,  $C_{1-6}$  alkylamino or di- $C_{1-6}$  alkylamino; and

$R^7$  represents  $C_{1-6}$  alkyl,

or a pharmaceutically-acceptable salt thereof,

provided that, when  $X_1$ ,  $X_3$  and  $X_4$  all represent  $-CH-$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  all  
10 represent  $-CH-$ ,  $Z_1$  represents  $-S-$  or  $-CH=CH-$ ,  $Z_2$  represents  $-CH-$  and  $R^5$  represents *n*-butyl or *iso*-butyl, then  $R^4$  does not represent  $-S(O)_2N(H)C(O)R^6$ , in which  $R^6$  represents  $-O$ -*n*-butyl,  $-O$ -*iso*-propyl,  $-O$ -*iso*-butyl or  $-CH_2-O$ -*n*-butyl,

which compounds and salts are referred to together hereinafter as "the  
15 compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the  
20 invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo* or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of  
25 a salt with another counter-ion, for example using a suitable ion exchange resin.

Unless otherwise specified, alkyl groups, and the alkyl parts of alkoxy, alkoxyalkyl and alkylamino groups, as defined herein may be straight-chain  
30 or, when there is a sufficient number (i.e. a minimum of three) of carbon

atoms, be branched-chain, and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic/acyclic. Such alkyl groups, and alkyl parts of alkoxy, alkoxyalkyl and alkylamino groups, may also be saturated or, when there is  
5 a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated. Unless otherwise specified, such groups may also be substituted by one or more halo, and especially fluoro, atoms.

For the avoidance of doubt, alkoxy groups are attached to the rest of the  
10 molecule *via* the oxygen atom in that group, alkylamino groups are attached to the rest of the molecule *via* the nitrogen atom of the amino part of that group and alkoxyalkyl groups are attached to the rest of the molecule *via* the alkyl part of that group.

15 The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

For the avoidance of doubt, the ring systems in compounds of formula I that comprise the groups  $Z_1$  and  $Z_2$ , are aromatic in nature. In some instances, for example in cases where one or more of  $Z_1$  and  $Z_2$  represent  $-CH-$  or  $-N-$   
20 the skilled person will appreciate that an additional H atom may necessarily be bonded to that CH group or N atom, in order to ensure that the rules of valency are adhered to. Preferred ring systems comprising the substituents  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  include phenyl groups, pyridinyl groups, pyrimidinyl groups, pyrazinyl groups and pyridazinyl groups. Preferred ring systems  
25 comprising the substituents  $Z_1$  and  $Z_2$  include phenyl groups, pyridinyl groups, thiophenyl groups and furanyl groups.

In this respect, compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the  
30 invention.

Compounds of the invention also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

15

Preferred compounds of the invention include those in which:

- (i) when  $X_1$  represents  $-C(R^1)-$ , then:
  - (a) when  $X_3$  represents  $-C(R^2)-$ , then  $X_4$  represents  $-N-$ ;
  - (b)  $X_3$  and  $X_4$  both represent  $N$ ; or
  - (c)  $X_3$  represents  $-C(R^2)-$  and  $X_4$  represents  $-C(R^3)-$ ; or
- (ii) when  $X_1$  represents  $-N-$ , then  $X_3$  represents  $-N-$ .

20

In case (i)(a) above, it is further preferred that  $R^1$  represents  $H$ .

In case (ii) above, when  $X_4$  represents  $-C(R^3)-$ , it is further preferred that  $R^3$  represents  $H$ .

25

Preferred compounds of formula I include those in which:

- $R^1$  represents  $C_{1-3}$  alkyl, such as ethyl, or, especially,  $H$ ;
- $R^2$  represents  $C_{1-3}$  alkyl, halo or, especially,  $H$ ;

30

$R^3$  represents  $C_{1-3}$  alkyl, halo or, especially, H;

$Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  all represent  $-CH-$ ;

$Z_1$  represents  $-S-$  or  $-CH=CH-$ ;

$Z_2$  represents  $-CH-$ ;

5  $R^4$  represents  $S(O)_2N(H)C(O)R^6$ ;

$R^5$  represents *n*-butyl or, particularly, *iso*-butyl;

$R^6$  represents *n*-butoxymethyl, *iso*-butoxy and especially, *n*-butoxy.

10 Preferred ring systems comprising the substituents  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  include imidazole groups, 1,2,4-triazole groups and tetrazole groups.

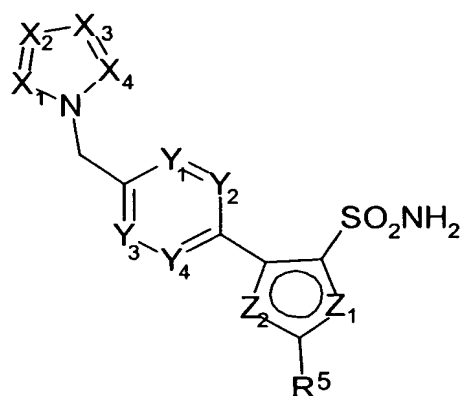
More preferred compounds of the invention include the compounds of the examples described hereinafter.

15 Compounds of formula I may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

20

(i) for compounds of formula I in which  $R^4$  represents  $-S(O)_2N(H)C(O)R^6$  and  $R^6$  is as hereinbefore defined, reaction of a compound of formula II,



II

wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined with a compound of formula III,



III

wherein  $L^1$  represents a suitable leaving group, such as halo (e.g. chloro or bromo) and  $R^6$  is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, di-*iso*-propylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, or mixtures thereof) and an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, trifluoromethylbenzene or triethylamine);

(ii) for compounds of formula I in which  $R^6$  represents  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl, coupling of a compound of formula II as hereinbefore defined with a compound of formula IV,

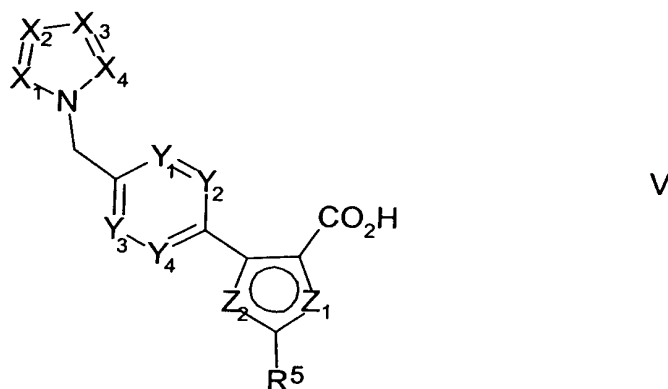


IV

wherein  $R^{6a}$  represents  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl, for example in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyl-diimidazole,  $N,N'$ -

dicyclohexylcarbodiimide, N,N'-disuccinimidyl carbonate, benzotriazole-1-yloxytris(dimethylamino)phosphoniumhexafluorophosphate, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosponium hexafluorophosphate or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate), a suitable base (as mentioned in process step (i) above) and an appropriate solvent (as mentioned in process step (i) above);

- 10 (iii) for compounds of formula I in which  $R^4$  represents  $-C(O)N(H)S(O)_2R^6$  and  $R^6$  is as hereinbefore defined, coupling of a compound of formula V,



- 15 wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined with a compound of formula VI,

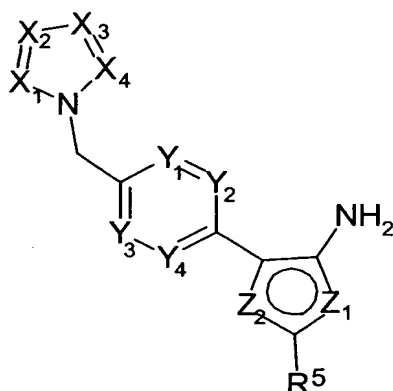


- 20 wherein  $R^6$  is as hereinbefore defined, for example in the presence of a suitable coupling reagent (such as those described in process step (ii) hereinbefore), and under similar reaction conditions to those described



hereinbefore for preparation of compounds of formula I in which  $R^6$  represents  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl;

- (iv) for compounds of formula I in which  $R^4$  represents  
 5  $-N(H)S(O)_2N(H)C(O)R^7$  and  $R^7$  is as hereinbefore defined, reaction of a compound of formula VII,



VII

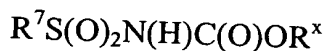
- 10 wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined with a compound of formula VIII,



VIII

- 15 wherein  $R^7$  is as hereinbefore defined, for example at or around room temperature in the presence of a suitable base (e.g. sodium hydroxide or triethylamine) and a suitable organic solvent (e.g. benzene or dichloromethane);

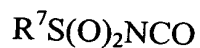
- 20 (v) for compounds of formula I in which  $R^4$  represents  $-N(H)C(O)N(H)S(O)_2R^7$  and  $R^7$  is as hereinbefore defined, reaction of a compound of formula VII as hereinbefore defined with a compound of formula IX,



IX

wherein  $R^x$  represents  $C_{1-2}$  alkyl and  $R^7$  is as hereinbefore defined, for  
 5 example at or around room temperature in the presence of a suitable organic  
 solvent (e.g. dichloromethane); or

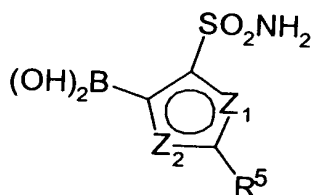
(vi) for compounds of formula I in which  $R^4$  represents  
 $-N(H)C(O)N(H)S(O)_2R^7$  and  $R^7$  is as hereinbefore defined, reaction of a  
 10 compound of formula VII as hereinbefore defined with an isocyanate  
 compound of formula X,



X

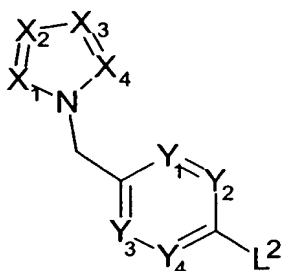
15 wherein  $R^7$  is as hereinbefore defined, for example at or around room  
 temperature in the presence of a suitable organic solvent (e.g.  
 dichloromethane).

Compounds of formula II may be prepared by reaction of a compound of  
 20 formula XI,



XI

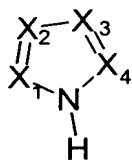
wherein  $R^5$ ,  $Z^1$  and  $Z^2$  are as hereinbefore defined, or a N-protected  
 25 derivative thereof, with a compound of formula XII,



XII

wherein  $L^2$  represents a suitable leaving group, such as trimethylsulphonate, or halo, such as iodo or bromo, and  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  are as  
 5 hereinbefore defined, for example in the presence of an appropriate coupling catalyst system (e.g. a palladium catalyst, such as  $Pd(PPh_3)_4$  or  $Pd(OAc)_2$  and a suitable base (e.g. sodium hydroxide, sodium carbonate, cesium carbonate, triethylamine or di-*iso*-propylamine)), as well as a suitable solvent system (e.g. toluene, ethanol, dimethoxymethane,  
 10 dimethylformamide, water, dioxane or mixtures thereof). This reaction may be carried out at above room temperature (e.g. at the reflux temperature of the solvent system that is employed). If a protected version of a compound of formula XI is employed, this reaction may be followed by deprotection of the  $SO_2NH$ -group under standard conditions, for example as described  
 15 hereinafter.

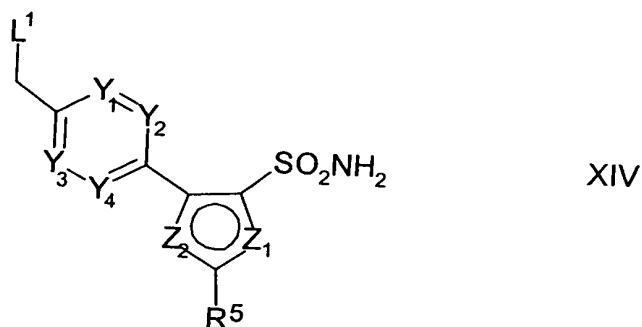
Compounds of formula II may alternatively be prepared by reaction of a compound of formula XIII,



XIII

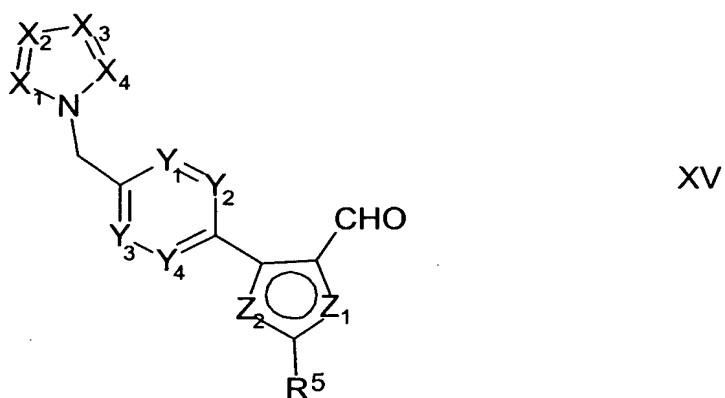
20

wherein  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  are as hereinbefore defined with a compound of formula XIV,



wherein  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$ ,  $R^5$  and  $L^1$  are as hereinbefore defined ( $L^1$ , in particular, may represent bromo), or a N-protected derivative thereof, for example at around or below room temperature in the presence of a suitable base (e.g. potassium hydroxide) and an appropriate organic solvent (e.g. DMSO). If a protected version of a compound of formula XIV is employed, this reaction may be followed by deprotection of the  $SO_2NH_2$ -group under standard conditions, for example as described hereinafter. Additionally, compounds of formula II in which  $Z_1$  is  $-CH=CH-$  and  $Z_2$  is  $-CH-$  may be prepared in this way, for example according, or analogously, to processes described in *inter alia* US patent number 5,312,820. Further, compounds of formula II in which  $Z_1$  is  $-S-$  and  $Z_2$  is  $-CH-$  may be prepared in this way for example according, or analogously, to processes described in *inter alia* UK patent application GB 2281298.

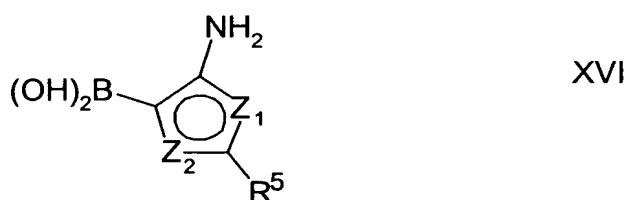
Compounds of formula V may be prepared by oxidation of a compound of formula XV,



wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined, for example under standard oxidation conditions in the presence of  
 5 a suitable oxidising agent, such as potassium permanganate or chromium (VI) oxide.

Compounds of formula VII may be prepared by reaction of a compound of formula XII as hereinbefore defined with a compound of formula XVI,

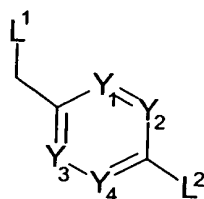
10



wherein  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined, or a N-protected derivative thereof, for example under similar conditions to those described  
 15 hereinbefore for preparation of compounds of formula II (first process). If a protected version of a compound of formula XVI is employed, this reaction may be followed by deprotection of the NH-group under standard conditions (e.g. acid hydrolysis).

20

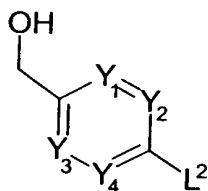
Compounds of formula XII may be prepared by standard techniques, for example by way of reaction of a compound of formula XIII as hereinbefore defined with a compound of formula XVII,



XVII

wherein  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $L^1$  and  $L^2$  are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formula II (second process).

Compounds of formula XIV are known in the art. For example, they may be prepared according, or analogously, to processes described in *inter alia* US patent number 5,312,820, UK patent application GB 2281298, and/or by reaction of a compound of formula XI as hereinbefore defined with a compound of formula XVIII,

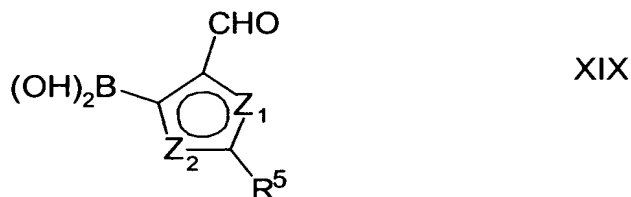


XVIII

wherein  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $L^2$  are as hereinbefore defined, for example under similar conditions to those described hereinbefore in respect of preparation of compounds of formula II (first process), followed by conversion of the OH group in the resultant intermediate to an appropriate leaving group,  $L^1$  (e.g., in the case where  $L^1$  is bromo, conversion may be carried out by reaction with  $CBr_4$ , for example at or around room

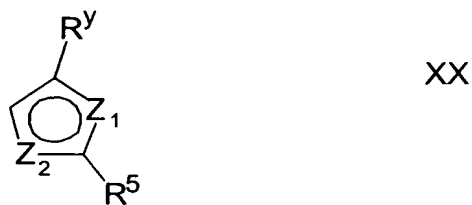
temperature in the presence of a base (e.g. triphenylphosphine) and a suitable organic solvent (e.g. DMF)).

Compounds of formula XV may be prepared by reaction of a compound of formula XII as hereinbefore defined with a compound of formula XIX,



wherein  $Z_1$ ,  $Z_2$  and  $R^5$  are as hereinbefore defined, or a protected (at the aldehyde part) derivative thereof, for example under similar conditions to those described hereinbefore for preparation of compounds of formula II (first process). If a protected version of a compound of formula XIX is employed, this reaction may be followed by deprotection of the CHO-group under standard conditions (e.g. acid hydrolysis).

Compounds of formulae XI, XVI and XIX and protected derivatives thereof may be prepared by reaction of a corresponding compound of formula XX,

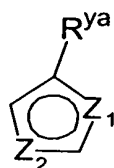


wherein  $R^y$  represents  $-S(O)_2NH_2$ ,  $-NH_2$  or  $-CHO$  (as appropriate) and  $R^5$ ,  $Z_1$  and  $Z_2$  are as hereinbefore defined, or an appropriate protected derivative thereof, with a reagent system that will enable the introduction of the  $-B(OH)_2$  into the appropriate ring system. Suitable reagent systems include

trialkylborates (e.g. tri-*iso*-propylborate). Such reactions may be carried out, for example, at low temperature (e.g. between  $-100^{\circ}\text{C}$  and  $0^{\circ}\text{C}$ , e.g. between  $-80^{\circ}\text{C}$  (such as  $-78^{\circ}\text{C}$ ) and  $-10^{\circ}\text{C}$  (such as  $-20^{\circ}\text{C}$ )) in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate organic solvent (e.g. THF), followed by acid hydrolysis (e.g. in the presence of dilute HCl).

Compounds of formula XX are available using known techniques. For example:

- (a) Compounds of formula XX in which  $\text{R}^y$  represents  $-\text{S}(\text{O})_2\text{NH}_2$ , or  $-\text{CHO}$ , and protected derivatives thereof, may be prepared by reaction of a compound of formula XXI,



XXI

wherein  $\text{R}^{ya}$  represents  $-\text{S}(\text{O})_2\text{NH}_2$ , or  $-\text{CHO}$  and  $\text{Z}_1$  and  $\text{Z}_2$  are as hereinbefore defined, or a protected derivative thereof, with a compound of formula XXII,

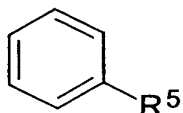


XXII

wherein  $\text{L}^3$  represents a suitable leaving group (such as toluenesulphonate, benzenesulphonate, methanesulphonate or halo, such as bromo or iodo) and  $\text{R}^5$  is as hereinbefore defined, for example at below room temperature (e.g. between around  $-35^{\circ}\text{C}$  and around  $-85^{\circ}\text{C}$ ), in the presence of a suitable base (e.g. *n*-butyl lithium) and an appropriate solvent (e.g. THF).



- (b) Compounds of formula XX in which  $R^y$  is  $-S(O)_2NH_2$ ,  $Z^1$  represents  $-CH=CH-$  and  $Z^2$  represents  $-CH-$ , and N-protected derivatives thereof, may be prepared by reaction of an appropriate compound of formula XXIII,



XXIII

wherein  $R^5$  is as hereinbefore defined with chlorosulphonic acid, followed by reaction of the resultant intermediate with ammonia, or a protected derivative thereof (e.g. *tert*-butylamine), under conditions that are well known to those skilled in the art.

- (c) Compounds of formula XX in which  $R^y$  is  $-CHO$ ,  $Z^1$  represents  $-CH=CH-$  and  $Z^2$  represents  $-CH-$ , and protected derivatives thereof, may be prepared by reaction of a compound of formula XXIII as hereinbefore defined with an appropriate reagent system for the introduction of an aldehyde group into the benzene ring (e.g.  $TiCl_4/CHCl_3$ ,  $SnCl_4/CH_2Cl_2$  or 1,3,5,7-azaadamantane/TFA) under standard reaction conditions, followed by (if appropriate) protection of the resultant benzaldehyde under standard conditions.

- (d) Compounds of formula XX in which  $R^y$  is  $-NH_2$ ,  $Z^1$  represents  $-CH=CH-$  and  $Z^2$  represents  $-CH-$ , and N-protected derivatives thereof, may be prepared by nitration of a compound of formula XXIII as hereinbefore defined, followed by reduction of the resultant nitrobenzene and (if appropriate) protection of the resultant

aminobenzene, all of which steps may be carried out under standard conditions.

Compounds of formulae III, IV, VI, VIII, IX, X, XIII, XVII, XVIII, XXI,  
5 XXII and XXIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

10

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes  
15 described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include sulphonamido, amino and aldehyde. Suitable protecting groups for sulphonamido and  
20 amino include *tert*-butoxycarbonyl, benzyloxycarbonyl, 2-trimethylsilylethoxycarbonyl (Teoc) or *tert*-butyl. Suitable protecting groups for aldehyde include alcohols, such as methanol or ethanol, and diols, such as 1,3-propanediol or, preferably, 1,2-ethanediol (so forming a cyclic acetal).

25

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are  
30 well known to those skilled in the art and as described hereinafter. For

example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques (e.g. using trifluoroacetic acid, sulfuric acid, toluenesulfonic acid or boron trichloride).

5

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

15

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

20

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3<sup>rd</sup> edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

### **Medical and Pharmaceutical Uses**

25

Compounds of the invention are useful because they possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, compounds of the invention are agonists of AngII, more particularly, are agonists of the AT2 receptor, and, especially, are selective agonists of that sub-receptor, for example as may be demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in those conditions in which endogenous production of AngII is deficient and/or where an increase in the effect of AngII is desired or required.

The compounds of the invention are further expected to be useful in those conditions where AT2 receptors are expressed and their stimulation is desired or required.

The compounds of the invention are further indicated in the treatment of conditions characterised by vasoconstriction, increased cell growth and/or differentiation, increased cardiac contractility, increased cardiovascular hypertrophy, and/or increased fluid and electrolyte retention.

The compounds of the invention are further indicated in the treatment of stress-related disorders, and/or in the improvement of microcirculation and/or mucosa-protective mechanisms.

Thus, compounds of the invention are expected to be useful in the treatment of disorders, which may be characterised as indicated above, and which are of, for example, the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system and the central nervous system (CNS).

Disorders of the gastrointestinal tract that may be mentioned include oesophagitis, gastric ulcers, duodenal ulcers, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome (IBS),  
 5 inflammatory bowel disease (IBD), pancreatitis, hepatitis, gall bladder disease, multiple organ failure (MOF) and sepsis. Other gastrointestinal disorders that may be mentioned include xerostomia, gastritis, gastroparesis, hyperacidity, disorders of the biliary tract, coeliacia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting,  
 10 nausea, indigestion and Sjögren's syndrome.

Disorders of the respiratory tract that may be mentioned include inflammatory disorders, such as asthma, obstructive lung diseases, pneumonitis, pulmonary hypertension and adult respiratory distress  
 15 syndrome.

Disorders of the kidneys that may be mentioned include renal failure, nephritis and renal hypertension.

20 Disorders of the eyes that may be mentioned include diabetic retinopathy, premature retinopathy and retinal microvascularisation.

Disorders of the female reproductive system that may be mentioned include ovulatory dysfunction.

25 Cardiovascular disorders that may be mentioned include hypertension, cardiac hypertrophy, cardiac failure, arteriosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post-balloon dilatation stenosis, angiogenesis, diabetic complications and  
 30 microvascular dysfunction.

Disorders of the CNS that may be mentioned include cognitive dysfunctions, dysfunctions of food intake (hunger/satiety) and thirst, stroke, cerebral bleeding, cerebral embolus and cerebral infarction.

5

Compounds of the invention may also be useful in the modulation of growth metabolism and proliferation, for example in the treatment of hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, the healing of ulcers, inhibition of adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer (e.g. in the  
10 gastrointestinal tract, lung cancer, etc), apoptosis, tumours (generally) and hypertrophy.

The compounds of the invention are indicated both in the therapeutic and/or  
15 prophylactic treatment of the above conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a condition in which endogenous production of AngII is deficient, and/or a condition where an increase in the effect of  
20 AngII is desired or required, and/or a condition where AT2 receptors are expressed and their stimulation is desired or required, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

25

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

30

When the condition to be treated is multiple organ failure, preferred routes of administration are parenteral (e.g. by injection). Otherwise, the preferred route of administration for compounds of the invention is oral.

- 5 The compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

10

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

- 15 According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

- Compounds of the invention may also be administered in combination with other AT2 agonists that are known in the art, as well as in combination with  
20 AT1 receptor antagonists that are known in the art, such as losartan.

According to a further aspect of the invention, there is provided a combination product comprising:

- (A) a compound of the invention; and  
25 (B) an AT1 receptor antagonist,  
wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

- Such combination products provide for the administration of compound of  
30 the invention in conjunction with AT1 receptor antagonist, and may thus be

presented either as separate formulations, wherein at least one of those formulations comprises compound of the invention and at least one comprises AT1 receptor antagonist, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including  
5 compound of the invention and AT1 receptor antagonist).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention  
10 and an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention,  
15 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

20 which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Depending upon the disorder and patient to be treated and the route of administration, the compounds of the invention may be administered at  
25 varying doses.

Although doses will vary from patient to patient, suitable daily doses are in the range of about 1 to 1000 mg per patient, administered in single or multiple doses. More preferred daily doses are in the range 2.5 to 250 mg  
30 per patient.



Individual doses of compounds of the invention may be in the range 1 to 100 mg.

5 In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of  
10 course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention have the advantage that they bind selectively to, and exhibit agonist activity at, the AT<sub>2</sub> receptor. By compounds which  
15 "bind selectively" to the AT<sub>2</sub> receptor, we include that the affinity ratio for the relevant compound (AT<sub>2</sub>:AT<sub>1</sub>) is at least 5:1, preferably at least 10:1 and more preferably at least 20:1.

The compounds of the invention may also have the advantage that they may  
20 be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art.

25

### **Biological Tests**

The following test procedures may be employed.

Test AReceptor Binding Assay using Rat Liver Membrane AT<sub>1</sub> Receptor

Rat liver membranes were prepared according to the method of Dudley *et al* (*Mol. Pharmacol.* (1990) **38**, 370). Binding of [<sup>125</sup>I]Ang II to membranes  
 5 was conducted in a final volume of 0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA (bovine serum albumin), liver homogenate corresponding to 5 mg of the original tissue weight, [<sup>125</sup>I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were incubated at 25°C for 1 h,  
 10 and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 4 × 2 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured in a gamma counter. The characteristics of the Ang II binding AT<sub>1</sub> receptor were determined by using six different concentrations (0.03-5  
 15 nmol/L) of the labeled [<sup>125</sup>I]AngII. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [<sup>125</sup>I]AngII. The dissociation constant ( $K_d = 1.7 \pm 0.1$  nM,  $[L] = 0.057$  nM) was determined by Scatchard analysis of data obtained with Ang II by using GraFit  
 20 (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate.

Test BReceptor Binding Assay using Porcine Myometrial Membrane AT<sub>2</sub> Receptor

Myometrial membranes were prepared from porcine uteri according to the method by Nielsen *et al* (*Clin. Exp. Pharm. Phys.* (1997) **24**, 309). Any possible interference that may be exhibited by binding of compound to AT<sub>1</sub> receptors was blocked by addition of 1 μM of a selective AT<sub>1</sub> inhibitor.  
 30 Binding of [<sup>125</sup>I]Ang II to membranes was conducted in a final volume of

0.5 mL containing 50 mM Tris-HCl (pH 7.4), 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 1 mM EDTA, 0.025% bacitracin, 0.2% BSA, homogenate corresponding to 10 mg of the original tissue weight, [<sup>125</sup>I]Ang II (70 000 cpm, 0.03 nM) and variable concentrations of test substance. Samples were  
5 incubated at 25°C for 1 h, and binding was terminated by filtration through Whatman GF/B glass-fiber filter sheets using a Brandel cell harvester. The filters were washed with 3 × 3 mL of Tris-HCl (pH 7.4) and transferred to tubes. The radioactivity was measured using a gamma counter. The characteristics of the Ang II binding AT<sub>2</sub> receptor was determined by using  
10 six different concentrations (0.03-5 nmol/L) of the labeled [<sup>125</sup>I]Ang II. Non-specific binding was determined in the presence of 1 μM Ang II. The specific binding was determined by subtracting the non-specific binding from the total bound [<sup>125</sup>I]Ang II. The dissociation constant ( $K_d = 0.7 \pm 0.1$  nM, [L] = 0.057 nM) was determined by Scatchard analysis of data obtained  
15 with Ang II by using GraFit (Erithacus Software, UK). The binding data were best fitted with a one-site fit. All experiments were performed at least in triplicate .

### Test C

#### 20 Duodenal Mucosal Alkaline Secretion Assay

Compounds were exposed to the duodenal mucosa in barbiturate-anaesthetised rats prepared for *in situ* titration of duodenal mucosal alkaline secretion, according to the methodology described by Flemström *et al* in *Am. J. Physiol.* (1982) **243**, G348.

25

The invention is illustrated by way of the following examples.

Example 1*N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide5 (a) *N*-*tert*-Butylthiophene-2-sulfonamide

Thiophene-2-sulfonyl chloride (15 g, 0.082 mol) was dissolved in CHCl<sub>3</sub> (200 mL) under N<sub>2</sub> atmosphere and then cooled to 0°C. *tert*-Butylamine (25.9 mL, 0.246 mol) dissolved in CHCl<sub>3</sub> (50 mL) was then added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at room  
 10 temperature and then at reflux for 10 min. Toluene (700 mL) was added and the organic phase was washed with water (3 x 50 mL), dried, and concentrated *in vacuo*. The sub-title product was used without further purification in the next step.

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 7.60(1H, dd, J=1.3, 3.8 Hz), 7.53(1H, dd, J=1.3, 5.0  
 15 Hz), 7.02(1H, dd, J=5.0, 3.8 Hz), 5.13(1H, m), 1.24 (9H, m)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

(b) 5-*iso*-Butyl-*N*-*tert*-butylthiophene-2-sulfonamide

*N*-*tert*-Butylthiophene-2-sulfonamide (10 g, 0.046 mol, see step (a) above)  
 20 was dissolved in THF (85 mL) under N<sub>2</sub> and then cooled to -78°C. *n*-BuLi (1.6 M, 76.9 mL, 0.12 mol) was added *via* a syringe. The reaction mixture was stirred at -78°C for 30 min. and then at -40°C for 2 h. Iodo-2-methylpropane (10.5 mL, 0.09 mol) was added dropwise to the reaction mixture. The reaction mixture was stirred overnight at room temperature.  
 25 The reaction was quenched with NH<sub>4</sub>Cl (aq.) and extracted with EtOAc. The combined organic phase was washed with brine and dried and concentrated *in vacuo*. The crude product was purified on column chromatography (hexanes:EtOAc (10:1)) to give the sub-title compound in 55% yield (7.0 g, 0.025 mol).

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.43(1H, d,  $J=3.6$  Hz), 6.67(1H, d,  $J=3.8$  Hz), 4.83(1H, m), 2.67(2H, d,  $J=7$  Hz), 1.88 (1H, m), 1.26(9H, m), 0.93(6H,  $J=6.6$  Hz).

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 145.0, 131.7, 131.2, 127.0, 55.1, 29.9

5 (c) 5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid

5-iso-Butyl-N-tert-butylthiophene-2-sulfonamide (10.6 g, 0.039 mol, see step (b) above) was dissolved in THF (165 mL) under  $\text{N}_2$  and then cooled to  $-78^\circ\text{C}$ .  $n\text{-BuLi}$  (1.6 M, 60.19 mL, 0.096 mol) was added *via* a syringe. The reaction mixture was stirred at  $-20^\circ\text{C}$  for 4 h. The tri-iso-propylborate (13.3  
10 mL, 0.058 mol) was then added *via* a syringe and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 2 M HCl (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with brine, dried and concentrated *in vacuo*. The product was used  
15 without further purification.

MS( $\text{ESI}^+$ )  $m/z$ : 236.8

(d) 3-(4-Hydroxymethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide

20 5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid (319.3 mg, 1.00 mmol, see step (c) above), 4-bromobenzyl alcohol (374.1 mg, 2.00 mmol), toluene (20 mL), ethanol (4 mL), NaOH (1.0M, 4 mL, 4 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (34 mg, 0.030mmol) were mixed together under  $\text{N}_2$ . The mixture was warmed to reflux for 2 hours and was then diluted with EtOAc (50  
25 mL), washed with water and brine and dried over  $\text{MgSO}_4$ . The solvent was removed and the residue was separated by column chromatography using  $\text{CHCl}_3$ :MeOH (40:1) as eluent to give 289 mg of the sub-title compound (yield: 76%).

IR(pure): 3465, 3162, 2952, 2867, 1441  $\text{cm}^{-1}$

$^1\text{H}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 7.59(2H, d,  $J = 8.2$  Hz), 7.45(2H, d,  $J = 8.2$  Hz), 6.75(1H, s), 4.75(2H, s), 4.11(1H, brs), 2.69(2H, d,  $J = 7.1$  Hz), 1.92(1H, m), 0.99(6H, d,  $J = 7.2$  Hz), 0.98(9H, s)

$^{13}\text{C}$  NMR  $\delta(\text{CD}_3\text{OD})$ : 148.3, 142.9, 141.1, 134.2, 130.3, 128.9, 127.6,  
5 126.8, 64.8, 54.5, 39.2, 30.5, 29.5, 22.1

MS( $\text{EI}^+$ )  $m/z$ : 382.0

Anal. Calcd for  $\text{C}_{19}\text{H}_{27}\text{NO}_3\text{S}_2$ : C, 59.8; H, 7.3; N, 3.7. Found: C, 59.6; H, 7.0; N, 3.5

10 (e) 3-(4-Bromomethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide

3-(4-Hydroxymethylphenyl)-5-*iso*-butyl-*N*-*tert*-butylthiophene-2-sulfonamide (280 mg, 0.734 mmol, see step (d) above) was dissolved in DMF (10 mL).  $\text{PPh}_3$  (459.2 mg, 1.75 mmol) and  $\text{CBr}_4$  (580.3, 1.75 mmol) were  
15 added to the resultant solution. The mixture was stirred for 24 h at room temperature and then diluted with ethyl acetate. The organic phase was washed with water (50 mL) and brine (50 mL) and then dried over  $\text{MgSO}_4$ . After removing the solvents, the residue was purified by column chromatography using hexane:acetone (5:1) as eluent to give the sub-title  
20 compound (314.9 mg, 0.709 mmol, 76% yield).

IR(pure): 3302, 2952, 2866, 1442  $\text{cm}^{-1}$

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 7.62(2H, d,  $J = 8.4$  Hz), 7.48(2H, d,  $J = 8.4$  Hz), 6.75(1H, s), 4.56(2H, s), 4.11(1H, brs), 2.69(2H, d,  $J = 7.1$  Hz), 1.92(1H, m), 0.99(6H, d,  $J = 7.2$  Hz), 0.98(9H, s)

25  $^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 148.5, 142.4, 138.2, 136.9, 135.1, 129.5, 129.1, 128.7, 54.6, 39.2, 32.8, 30.5, 29.5, 22.1

MS( $\text{EI}^+$ )  $m/z$ : 445.8

(f) 5-iso-Butyl-N-tert-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide

KOH (112.2 mg, 2.00 mmol, crushed pellets) was added to DMSO (10 mL, dried over 4A molecular sieve) and stirred for 5 min. Tetrazole (28.0 mg, 0.4 mmol) was added to the mixture, which was then stirred for 2 h. 3-(4-Bromomethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide (130 mg, 0.292 mmol, see step (e) above) was added, the mixture was cooled briefly and stirred for an additional hour before water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (250 mL) and the extract was washed with water (2 x 50 mL) and brine (50 mL). The organic phase was dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. The residue was purified on column chromatography using hexane:acetone (3:1) as eluent to give the sub-title compound (28.6 mg, 0.066 mmol, 23% yield). IR(pure): 3328, 3134, 2980, 1501, 1466 cm<sup>-1</sup>

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.52(1H, s), 7.64(2H, d, J= 8.3 Hz), 7.46(2H, d, J= 8.3 Hz), 6.73(1H, s), 5.85(2H, s), 2.69(2H, d, J= 7.1 Hz), 1.91(1H, m), 1.58(1H, s), 0.98(15H, brs)

<sup>13</sup>C NMR δ( CDCl<sub>3</sub>): 153.2, 148.5, 142.4, 136.8, 135.8, 133.2, 129.7, 128.8, 128.5, 56.3, 54.6, 39.2, 30.5, 29.5, 22.1

MS(EI<sup>+</sup>) m/z: 434.0

Anal. Calcd for C<sub>20</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub> × H<sub>2</sub>O: C, 53.2; H, 6.5; N, 15.5. Found: C, 53.7; H, 6.1; N, 15.2

(g) 5-iso-Butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

To a solution of 5-iso-butyl-N-tert-butyl-3-(4-tetrazol-2-ylmethylphenyl)-thiophene-2-sulfonamide (42.1 mg, 0.111 mmol, see step (f) above) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added BCl<sub>3</sub> (0.5 mL, 1M, 0.5 mmol) under N<sub>2</sub> (g). The reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over MgSO<sub>4</sub> and the

solvent was removed *in vacuo*. The crude product was used directly in the next step without further purification.

5 (h) *N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide

The crude product from step (g) above was dissolved in pyridine (1 mL, dried over 4Å molecular sieve). Pyrrolidinopyridine (14 mg, 0.0095 mmol) and butyl chloroformate (120 µL, 0.97 mmol) were added to the mixture, which was then stirred for 30 hours under N<sub>2</sub>(g) at room temperature. The solvent was removed *in vacuo* and then co-evaporated with acetonitrile. Purification using column chromatography with CHCl<sub>3</sub>:MeOH (35:1) as eluent yielded the title compound (24.9 mg, 0.052 mmol) in 54% yield (from 5-*iso*-butyl-*N*-*tert*-butyl-3-(4-tetrazol-2-ylmethylphenyl)thiophene-2-sulfonamide).

15 IR(pure): 3330, 2961, 2875, 1743, 1466 cm<sup>-1</sup>

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.49(1H, s), 7.68(1H, s), 7.48(2H, d, J= 8.2 Hz), 7.40(2H, d, J=8.2 Hz), 6.73(1H, s), 5.82(2H, s), 4.07(2H, t, J= 6.6 Hz), 2.70(2H, d, J= 7.1 Hz), 1.91(1H, m), 1.50(2H, m), 1.24(2H, m), 0.98(6H, d, J= 6.9 Hz), 0.87(3H, J= 7.4 Hz)

20 <sup>13</sup>C NMR δ( CDCl<sub>3</sub>): 153.2, 151.8, 150.1, 145.6, 134.8, 133.4, 129.6, 129.3, 128.3, 66.9, 56.3, 39.2, 30.5, 30.4, 22.2, 18.7, 13.6

MS(EI<sup>+</sup>) m/z: 478.0

Anal. Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub>S<sub>2</sub>: C, 52.8; H, 5.7; N, 14.7. Found: C, 53.0; H, 5.8; N, 14.1



Example 2*N*-Butyloxycarbonyl-5-*iso*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide5 (a) 1-(4-Bromobenzyl)-1*H*-tetrazole

Dimethyl sulphoxide (10 mL, dried over 4A molecular sieve) was added to potassium hydroxide (1.12 g, 0.02 mol, crushed pellets) and the mixture was stirred for 5 minutes. 1*H*-Tetrazole (0.35 g, 0.005 mol) was then added and the mixture was stirred for 2 hours. 4-Bromobenzyl bromide (1.87 g, 10 0.0075 mol) was added and the mixture was cooled briefly and stirred for a further hour before adding water (50 mL). The mixture was extracted with ether (3 × 80 mL) and each extract was washed with water (3 × 50 mL). The combined ether layers were dried over MgSO<sub>4</sub> and the solvent using removed *in vacuo*. The residue was chromatographed on silica gel with 15 CHCl<sub>3</sub>:MeOH (40:1) as eluent yielding the sub-title compound (0.98 g, yield: 82%).

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.64(1H, s), 7.50(2H, d, J= 8.4 Hz), 7.18(2H, d, J= 8.4), 5.56(2H, s)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 142.4, 132.4, 131.8, 129.9, 123.4, 51.3

20 MS(ESI<sup>+</sup>) m/z: 238.8

Anal. Calcd. for C<sub>8</sub>H<sub>7</sub>BrN<sub>4</sub>: C, 40.2; H, 3.0; N, 23.4. Found: C, 40.3; H, 3.0; N, 23.4

25 (b) 5-*iso*-Butyl-*N*-*tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

5-*iso*-Butyl-2-(*N*-*tert*-butylaminosulfonyl)thiophene-3-boronic acid (401.0 mg, 1.256 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1*H*-tetrazole (199.4 mg, 0.834 mmol, see step (a) above), toluene (20 mL), ethanol (3.0 mL), NaOH (1.0M, 5.0 mL, 5.0 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (29.0 mg, 0.25 mmol) 30 were mixed under N<sub>2</sub>. The mixture was warmed to reflux for 2 hours. The

mixture was diluted with EtOAc (20 mL), washed with water and brine, and dried over MgSO<sub>4</sub>. The solvent was removed and the residue was separated by column chromatography using CHCl<sub>3</sub>:MeOH (40:1) as eluent to give 222.4 mg of the sub-title compound (yield: 62%).

5 IR(pure): 3284, 3134, 2958, 2870, 1513, 1436 cm<sup>-1</sup>

<sup>1</sup>H NMR δ(CDCl<sub>3</sub>): 8.71(1H, s), 7.64(2H, d, J= 8.3 Hz), 7.40(2H, d, J= 8.3 Hz), 6.74(1H, s), 5.65(2H, s), 2.67(2H, d, J= 7.1 Hz), 1.94(1H, m), 0.99(15H, m)

<sup>13</sup>C NMR δ(CDCl<sub>3</sub>): 148.5, 142.6, 142.2, 136.8, 135.9, 133.1, 129.9, 128.8,  
10 128.3, 54.6, 51.7, 39.2, 30.5, 29.5, 22.1

MS(ESI<sup>+</sup>) m/z: 433

(c) 5-iso-Butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

BCl<sub>3</sub> (1.0 mL, 1M, 1.0 mmol) was added to a solution of 5-iso-butyl-*N-tert*-  
15 butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide (177.0 mg, 0.408 mmol, see step (b) above) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under N<sub>2</sub> (g), and the reaction mixture was stirred for 0.5 h. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine, dried over MgSO<sub>4</sub> and the solvent  
20 was removed *in vacuo*. The crude product was used directly in the next step used without further purification.

(d) N-Butyloxycarbonyl-5-iso-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide

25 The title compound was prepared (89.6 mg, 0.188 mmol, 46% yield (from 5-iso-butyl-*N-tert*-butyl-3-(4-tetrazol-1-ylmethylphenyl)thiophene-2-sulfonamide)) analogously to the procedure described in Example 1(h) above from the crude 5-iso-butyl-3-(4-tetrazol-1-ylmethylphenyl)-thiophene-2-sulfonamide from step (c) above.

30 IR(pure): 3135, 2959, 2875, 1747, 1464 cm<sup>-1</sup>

$^1\text{H}$  NMR  $\delta(\text{CDCl}_3)$ : 8.73(1H, s), 7.43(2H, d,  $J = 7.7$  Hz), 7.24(2H, d,  $J = 7.7$  Hz), 6.72(1H, s), 5.59(2H, s), 4.00(2H, brs), 2.69(2H, brs), 1.91(1H, m), 1.46(2H, m), 1.19(2H, m), 0.95(6H, d,  $J = 6.9$  Hz), 0.83(3H,  $J = 6.8$  Hz)

$^{13}\text{C}$  NMR  $\delta(\text{CDCl}_3)$ : 151.8, 151.4, 145.3, 143.0, 134.8, 133.5, 129.6, 129.1,  
5 127.8, 66.9, 51.4, 39.2, 30.9, 30.4, 22.2, 18.7, 13.6

MS(EI<sup>+</sup>)  $m/z$ : 478.0

Anal. Calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_5\text{O}_4\text{S}_2 \times \frac{1}{2} \text{H}_2\text{O}$ : C, 51.8; H, 5.8; N, 14.4. Found: C, 51.4; H, 5.6; N, 14.1

### 10 Example 3

*N*-Butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-*iso*-butyl-thiophene-2-sulfonamide

(a) 1-(4-Bromo-benzyl)-1*H*-[1,2,4]triazole

15 DMF and KOH (3.3 g, 58 mmol) were stirred together at rt for 5 minutes before adding 1,2,4-triazole (1 g, 14.5 mmol). After a further 30 minutes, the reaction mixture was cooled to 0°C and 1-bromo-4-bromomethylbenzene (7.2 g, 29 mmol) was added dropwise over 5 minutes. The reaction mixture was heated to 60°C, then cooled to rt, extracted with ethyl acetate  
20 and water, and subsequently dried over  $\text{K}_2\text{CO}_3$ . The solvent was evaporated to yield yellow-white crystals, which, upon repeated recrystallisation, (ethylacetate/isohexane) yielded 0.60 g of the sub-title compound as white crystals (62% isolated yield).

$^1\text{H}$  NMR  $\delta(270 \text{ MHz}, \text{CDCl}_3)$ : 8.11 (s, 1H), 7.96 (s, 1H), 7.51-7.38 (m, 2H),  
25 7.15-7.10 (m, 2H), 5.29 (s, 2H)

$^{13}\text{C}$  NMR  $\delta(67.8 \text{ MHz}, \text{CDCl}_3)$ : 152.2, 143.0, 133.5, 132.1, 129.5, 122.7, 52.8

MS  $m/z$  238 ( $\text{M}^+ + 1$ )

(b) 3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide

5-iso-Butyl-2-(N-tert-butylaminosulfonyl)thiophene-3-boronic acid (0.479 g, 1.5 mmol, see Example 1(c) above), 1-(4-bromobenzyl)-1H-  
 5 [1,2,4]triazole (0.238 g, 1 mmol, see step (a) above), Pd(OAc)<sub>2</sub> (15.7 mg, 0.03 mmol), triphenyl phosphine (15.7 mg, 0.06 mmol) and NaOH (0.16 g, 4 mmol) were dissolved in 4 mL of toluene/ethanol (4:1) in a thick walled glass tube, and were then heated to 80°C for 1 h. The reaction mixture was cooled to rt, extracted with ethyl acetate and water and subsequently dried  
 10 over K<sub>2</sub>CO<sub>3</sub>. The solvent was evaporated and the reaction mixture was separated on a silica column (dichloromethane + 1% methanol to dichloromethane + 4% methanol) to yield 0.288 g of the sub-title compound (65% yield).

<sup>1</sup>H NMR δ(270 MHz, CDCl<sub>3</sub>): 8.13 (s, 1H), 7.94 (s, 1H), 7.60-7.57 (m, 2H), 7.33-7.30 (m, 2H), 6.72 (s, 1H), 5.37 (s, 2H), 4.47 (s, 1H), 2.65 (d, *J* = 7 Hz, 2H), 1.89 (sept *J* = 7 Hz, 1H), 0.96 (s, 9H), 0.94 (d, *J* = 7 Hz, 6H)

<sup>13</sup>C NMR δ(67.8 MHz, CDCl<sub>3</sub>): 152.1, 148.5, 143.1, 142.3, 136.6, 135.2, 134.8, 129.6, 128.8, 128.0, 54.5, 53.1, 39.1, 30.4, 29.4, 22.1

MS *m/z* 433 (*M*<sup>+</sup> + 1)

20

(c) 3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

3-(4-[1,2,4]Triazol-1-ylmethylphenyl)-5-iso-butyl-N-tert-butylthiophene-2-sulfonamide (146.4 mg, 0.34 mmol, see step (b) above) was mixed with  
 25 BCl<sub>3</sub> (1M solution in hexane) (2 mL, 1.7 mmol) in 5 mL of dichloromethane at rt and stirred for 1 h. The reaction mixture was extracted with ethyl acetate and water and subsequently dried over K<sub>2</sub>CO<sub>3</sub>. The solvent was evaporated and the resultant product was sufficiently pure to be used directly in the next step.

30

(d) N-Butyloxycarbonyl-3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide

59 mg (0.16 mmol) of the crude 3-(4-[1,2,4]triazol-1-ylmethylphenyl)-5-iso-butylthiophene-2-sulfonamide from step (c) above was mixed with butyl chloroformate (31  $\mu$ L, 0.24 mmol) and DMAP (2 mg, 16  $\mu$ mol) in 5 mL of triethylamine at 0°C. The reaction mixture was stirred overnight and then diluted with ethyl acetate, washed with water and dried over K<sub>2</sub>CO<sub>3</sub>. The reaction mixture was then separated on a silica column (dichloromethane + 15% methanol), circular chromatography (dichloromethane + 10-15% methanol and preparative LC-MS to yield 7.0 mg of the title compound (9 % isolated yield).

<sup>1</sup>H NMR  $\delta$ (270 MHz, CDCl<sub>3</sub>): 8.11 (s, 1H), 7.98 (s, 1H), 7.50-7.47 (m, 2H), 7.29-7.26 (m, 2H), 6.74 (s, 1H), 5.39 (s, 2H), 4.05 (t, *J* = 7 Hz, 2H), 2.71 (d, *J* = 7 Hz, 2H), 1.95 (sept, *J* = 7 Hz, 1H), 1.52 (pent, *J* = 7 Hz, 2H), 1.26 (sext, *J* = 7 Hz, 2H), 0.99 (d, *J* = 7 Hz, 6H), 0.88 (t, *J* = 7 Hz, 3H)

<sup>13</sup>C NMR  $\delta$ (67.8 MHz, CDCl<sub>3</sub>): 151.9, 151.1, 145.1, 143.4, 134.7, 134.2, 131.6, 129.7, 129.0, 127.8, 66.3, 53.2, 39.2, 30.4, 30.3, 22.1, 18.7, 13.5

MS *m/z* (relative intensity 30 eV) 477 (M<sup>+</sup> + 1)

20 Example 4

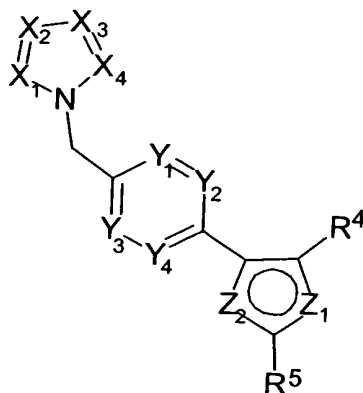
Title compounds of the Examples were tested in Tests A and B above and were found to exhibit an affinity for AT2 receptors of at least K<sub>i</sub> = 50 nM and an affinity to AT1 receptors of less than K<sub>i</sub> = 1  $\mu$ M.

25 Example 5

Title compounds of the Examples are tested in Test C above and are found to stimulate markedly mucosal alkalisation. This effect is blocked by co-administration of the selective AT2 receptor antagonist PD123319 (Sigma Chemical Company).

# Claims

1. A compound of formula I,



5

wherein

one of  $X_1$  and  $X_2$  represents  $-N-$  and the other represents  $-C(R^1)-$ ;

$X_3$  represents  $-N-$  or  $-C(R^2)-$ ;

- 10  $X_4$  represents  $-N-$  or  $-C(R^3)-$ ;

$R^1$ ,  $R^2$  and  $R^3$  independently represent H,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl or halo;

provided that, when  $X_1$  represents  $-C(R^1)-$ ,  $X_3$  represents  $-C(R^2)-$  and  $X_4$  represents  $-C(R^3)-$ , then  $R^1$  represents H;

- 15  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  represent  $-CH-$ ,  $-CF-$  or  $-N-$ , provided that, at any one time, no more than two of  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  may represent  $-N-$ ;

$Z_1$  represents  $-CH-$ ,  $-O-$ ,  $-S-$ ,  $-N-$  or  $-CH=CH-$ ;

$Z_2$  represents  $-CH-$ ,  $-O-$ ,  $-S-$  or  $-N-$ ;

provided that:

- 20 (a)  $Z_1$  and  $Z_2$  are not the same;
- (b) when  $Z_1$  represents  $-CH=CH-$ , then  $Z_2$  may only represent  $-CH-$  or  $-N-$ ; and

(c) when one  $Z_1$  and  $Z_2$  represents  $-\text{CH}-$ , then the other represents  $-\text{O}-$  or  $-\text{S}-$ ;

$R^4$  represents  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^6$ ,  $-\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^6$ , or, when  $Z_1$  represents  $-\text{CH}=\text{CH}-$ ,  $R^4$  may represent  $-\text{N}(\text{H})\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^7$  or

5  $-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^7$ ; and

$R^5$  represents  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy or  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$ -alkyl;

$R^6$  represents  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$ -alkyl,  $\text{C}_{1-6}$  alkylamino or di- $\text{C}_{1-6}$  alkylamino; and

$R^7$  represents  $\text{C}_{1-6}$  alkyl,

10 or a pharmaceutically-acceptable salt thereof,

provided that, when  $X_1$ ,  $X_3$  and  $X_4$  all represent  $-\text{CH}-$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$  and  $Y_4$  all represent  $-\text{CH}-$ ,  $Z_1$  represents  $-\text{S}-$  or  $-\text{CH}=\text{CH}-$ ,  $Z_2$  represents  $-\text{CH}-$  and  $R^5$  represents *n*-butyl or *iso*-butyl, then  $R^4$  does not represent  $-\text{S}(\text{O})_2\text{N}(\text{H})\text{C}(\text{O})\text{R}^6$ , in which  $R^6$  represents  $-\text{O}-n$ -butyl,  $-\text{O}-iso$ -propyl,  $-\text{O}-$   
15 *iso*-butyl or  $-\text{CH}_2-\text{O}-n$ -butyl.

2. A compound as claimed in Claim 1 wherein, when  $X_1$  represents  $-\text{C}(\text{R}^1)-$ , and  $X_3$  represents  $-\text{C}(\text{R}^2)-$ , then  $X_4$  represents  $-\text{N}-$ .

20 3. A compound as claimed in Claim 2 wherein  $\text{R}^1$  represents H.

4. A compound as claimed in Claim 1 wherein, when  $X_1$  represents  $-\text{C}(\text{R}^1)-$ , then  $X_3$  and  $X_4$  both represent N.

25 5. A compound as claimed in Claim 1 wherein, when  $X_1$  represents  $-\text{C}(\text{R}^1)-$ , then  $X_3$  represents  $-\text{C}(\text{R}^2)-$  and  $X_4$  represents  $-\text{C}(\text{R}^3)-$ .

6. A compound as claimed in Claim 1, wherein, when  $X_1$  represents  $-\text{N}-$ , then  $X_3$  represents  $-\text{N}-$ .

7. A compound as claimed in Claim 6 wherein, when  $X_4$  represents  $-C(R^3)-$ , then  $R^3$  represents H.
8. A compound as claimed in any one of Claims 1, 2 or 4 to 7, wherein  
5  $R^1$  represents H or  $C_{1-3}$  alkyl.
9. A compound as claimed in Claim 8, wherein  $R^1$  represent H or ethyl.
10. A compound as claimed in any one of Claims 1 to 3, 5, 8 or 9  
10 wherein  $R^2$  represents  $C_{1-3}$  alkyl, halo or H.
11. A compound as claimed in Claim 10 wherein  $R^2$  represents H.
12. A compound as claimed in any one of Claims 1, 5, 6 or 8 to 10  
15 wherein  $R^3$  represents  $C_{1-3}$  alkyl, halo or H.
13. A compound as claimed in Claim 12 wherein  $R^3$  represents H.
14. A compound as claimed in any one of the preceding claims wherein  
20  $Y_1, Y_2, Y_3$  and  $Y_4$  all represent  $-CH-$ .
15. A compound as claimed in any one of the preceding claims wherein  
 $Z_1$  represents  $-S-$  or  $-CH=CH-$ .
- 25 16. A compound as claimed in any one of the preceding claims wherein  
 $Z_2$  represents  $-CH-$ .
17. A compound as claimed in any one of the preceding claims wherein  
 $R^4$  represents  $S(O)_2N(H)C(O)R^6$ .



18. A compound as claimed in any one of the preceding claims wherein R<sup>5</sup> represents *n*-butyl or *iso*-butyl.
19. A compound as claimed in any one of the preceding claims wherein  
5 R<sup>6</sup> represents *n*-butoxymethyl, *iso*-butoxy or *n*-butoxy.
20. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10 21. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.
22. A compound as defined in any one of Claims 1 to 19, or a  
15 pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.
23. A compound as defined in any one of Claims 1 to 19, or a  
20 pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which endogenous production of AngII is deficient.
24. A compound as defined in any one of Claims 1 to 19, or a  
25 pharmaceutically acceptable salt thereof, for use in the treatment of a condition in which an increase in the effect of AngII is desired or required.
25. A compound as defined in any one of Claims 1 to 19, or a  
30 pharmaceutically acceptable salt thereof, for use in the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

26. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which selective agonism of the AT2 receptor is desired and/or required.

27. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which endogenous production of AngII is deficient.

28. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition in which an increase in the effect of AngII is desired or required.

29. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a condition where AT2 receptors are expressed and their stimulation is desired or required.

30. The use as claimed in any one of Claims 26 to 29, wherein the condition is of the gastrointestinal tract, the cardiovascular system, the respiratory tract, the kidneys, the eyes, the female reproductive (ovulation) system, or the central nervous system.

31. The use as claimed in Claim 30, wherein the condition is oesophagitis, a gastric ulcer, a duodenal ulcer, dyspepsia (including non-ulcer dyspepsia), gastro-oesophageal reflux, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, hepatitis, gall bladder disease, multiple organ failure,

sepsis, xerostomia, gastritis, gastroparesis, hyperacidity, a disorder of the biliary tract, coeliacia, Crohn's disease, ulcerative colitis, diarrhoea, constipation, colic, dysphagia, vomiting, nausea, indigestion, Sjögren's syndrome, inflammatory disorders, asthma, an obstructive lung disease, pneumonitis, pulmonary hypertension, adult respiratory distress syndrome, renal failure, nephritis, renal hypertension, diabetic retinopathy, premature retinopathy, retinal microvascularisation, ovulatory dysfunction, hypertension, cardiac hypertrophy, cardiac failure, arteriosclerosis, arterial thrombosis, venous thrombosis, endothelial dysfunction, endothelial lesions, post balloon dilatation stenosis, angiogenesis, diabetic complications, microvascular dysfunction, cognitive dysfunctions, dysfunctions of food intake (hunger/satiety), thirst, stroke, cerebral bleeding, cerebral embolus, cerebral infarction, hypertrophic disorders, prostate hyperplasia, autoimmune disorders, psoriasis, obesity, neuronal regeneration, an ulcer, adipose tissue hyperplasia, stem cell differentiation and proliferation, cancer, apoptosis, tumours or hypertrophy.

32. The use as claimed in Claim 31, wherein the condition is non-ulcer dyspepsia, irritable bowel syndrome, multiple organ failure, hypertension or cardiac failure.

33. A method of treatment of a condition in which selective agonism of the AT<sub>2</sub> receptor is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

34. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, and an

AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

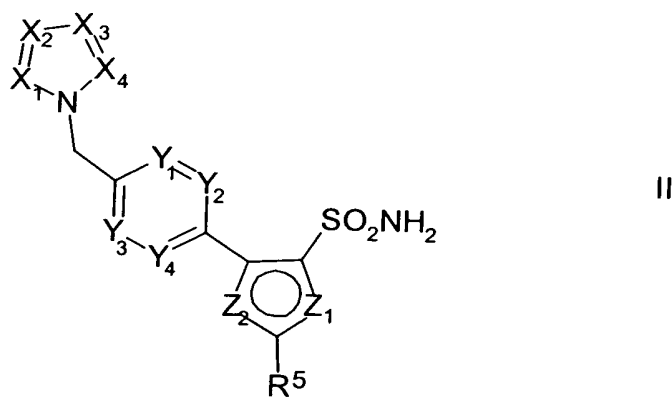
35. A kit of parts comprising components:

- 5 (a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and
- 10 (b) a pharmaceutical formulation including an AT1 receptor antagonist, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

15 36. A process for the preparation of a compound as defined in Claim 1, which comprises:

- (i) for compounds of formula I in which  $R^4$  represents  $-S(O)_2N(H)C(O)R^6$  and  $R^6$  is as defined in Claim 1, reaction of a compound of formula II,



20 wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as defined in Claim 1 with a compound of formula III,



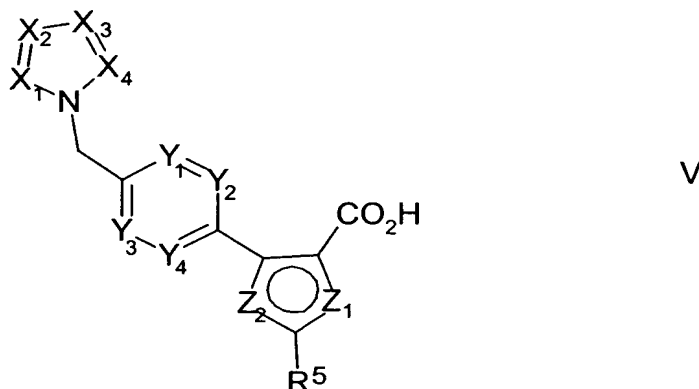
wherein  $L^1$  represents a suitable leaving group and  $R^6$  is as defined in Claim 1;

- (ii) for compounds of formula I in which  $R^6$  represents  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl, coupling of a compound of formula II as defined above with a  
5 compound of formula IV,



wherein  $R^{6a}$  represents  $C_{1-6}$  alkoxy- $C_{1-6}$ -alkyl;

- (iii) for compounds of formula I in which  $R^4$  represents  $-C(O)N(H)S(O)_2R^6$  and  $R^6$  is as defined in Claim 1, coupling of a compound of formula V,



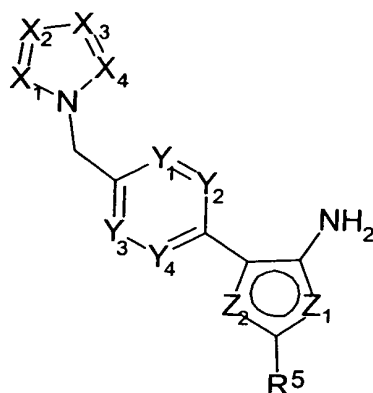
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wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as defined in Claim 1, with a compound of formula VI,



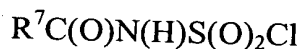
wherein  $R^6$  is as defined in Claim 1;

- (iv) for compounds of formula I in which  $R^4$  represents  
15  $-N(H)S(O)_2N(H)C(O)R^7$  and  $R^7$  is as defined in Claim 1, reaction of a compound of formula VII,



VII

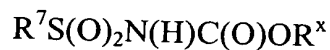
wherein  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$ ,  $Z_1$ ,  $Z_2$  and  $R^5$  are as defined in Claim 1, with a compound of formula VIII,



VIII

5 wherein  $R^7$  is as defined in Claim 1;

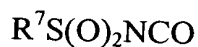
(v) for compounds of formula I in which  $R^4$  represents  $-N(H)C(O)N(H)S(O)_2R^7$  and  $R^7$  is as defined in Claim 1, reaction of a compound of formula VII as defined above with a compound of formula IX,



IX

10 wherein  $R^x$  represents  $C_{1-2}$  alkyl and  $R^7$  is as defined in Claim 1; or

(vi) for compounds of formula I in which  $R^4$  represents  $-N(H)C(O)N(H)S(O)_2R^7$  and  $R^7$  is as defined in Claim 1, reaction of a compound of formula VII as defined above with a compound of formula X,



X

15 wherein  $R^7$  is as defined in Claim 1.

37. A compound of formula II as defined in Claim 36 or a protected derivative thereof.

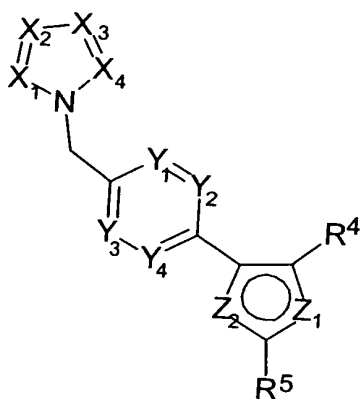
20 38. A compound of formula V as defined in Claim 36 or a protected derivative thereof.

39. A compound of formula VII as defined in Claim 36 or a protected derivative thereof.

**ABSTRACT**

There is provided a compound of formula I,

5



I

wherein X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, Y<sub>4</sub>, Z<sub>1</sub>, Z<sub>2</sub>, R<sup>4</sup> and R<sup>5</sup> have meanings  
 given in the description, and pharmaceutically-acceptable salts thereof,  
 10 which compounds are useful as selective agonists of the AT<sub>2</sub> receptor, and  
 thus, in particular, in the treatment of *inter alia* gastrointestinal conditions,  
 such as dyspepsia, IBS and MOF, and cardiovascular disorders.